

REMARKS

Claims 34, 42, and 45-46 are pending in this application. Claims 1-33, 35-41, 43 and 44 have been cancelled.

The Examiner has rejected Claims 34, 36, 38, 42, 45, and 46 under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614) and further in view of Jain et al. (US/200200126675).

According to the Examiner, Nadkarni discloses rapidly disintegrating multiparticulate controlled release formulations of lamotrigine or a pharmaceutically acceptable salt in a core to provide better control of blood plasma level (Abstract). The Examiner further points out that, while Nadkarni does not teach the thickness of outer coating or outer coating with one or more orifices, Staniforth does. It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time of the invention to make a sustained release formulation of lamotrigine with an outer coat covering said core impermeable to environmental fluids because of the teachings of Nadkarni and Staniforth.

The Examiner also notes that neither of the references explicitly teaches the outer coat dissolves when the surrounding pH exceeds 5, but points out that one of ordinary skill would be motivated to use the appropriate pH that would simulate *in vivo* conditions to get an idea of how the composition would behave in the human body. The Examiner concludes that it is within the level of ordinary skill in the art to manipulate the formulation and pH parameters to achieve the desired release profile over a range of pH environments. While the Examiner points out that the references (Nadkarni and Staniforth) do not explicitly teach the rate-retarding polymer HPMC, he cites Jain et al. as disclosing a nanoparticulate formulation in which the nanoparticulate agent can be lamotrigine and the release retarding polymer can be hydroxypropyl methyl cellulose (HPMC).

The Examiner notes that the Jain reference does not teach a value for the thickness of the outer coat polymer as claimed in Claim 38. However, the Examiner cites Staniforth as providing motivation to do so (col. 7, lines 3-13).

Hence, adjusting the thickness of the outer coat could be accomplished by routine experimentation according to Staniforth.

The Examiner points out that the reference does not teach the AUC values or the Cmax values after administration of sustained release formulation of lamotrigine as in Claim 42.

It is the Examiner's assertion that it would have been obvious to one of ordinary skill in the art that the sustained formulation comprising lamotrigine having a Cmax less than the instant release tablet containing the same amount of lamotrigine because Nadkarni teaches that the controlled release lamotrigine is designed to avoid excessive Cmax levels will produce lower plasma concentration, which are reached over a longer period of time. Also, according to the Examiner it is obvious to one of ordinary skill in the art that the sustained release formulation comprising the same composition taught by the teachings of Nadkarni and Staniforth will have the same release profile and properties such as AUC and Cmax values.

The Argument

It is Applicants' position that the formulations embodied in amended Claims 34, 36, 38, 42, 45, and 46 are not obvious under 35 USC 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004, 614) and further in view of Jain et al. (U.S. 2002/0012675, effective filing date June 12, 1999).

Nadkarni (WO 03/104192) discloses a rapidly disintegrating multiparticulate controlled release formulation of particles of lamotrigine that is administered one or more times a day (Abstract). The Nadkarni multiparticulate formulation has been designed to provide lamotrigine that can be taken without water or can be dispersed in water for the convenience of patients (Nadkarni, page 3, lines 29-33; page 5, first paragraph). The multiparticulate formulation is made up of a release rate controlling polymer, a rapidly disintegrating binder, and particles of lamotrigine.

Nadkarni's multiparticulate formulation is not formulated like Applicants', In Nadkarni, lamotrigine and excipient(s) are made to form discrete core particles, each of which is then layered with one or more different rate controlling polymers or membranes (Nadkarni, claim 2). Preferably the core particle is built around inert nuclei or bases (e.g., sugar) (Nadkarni, page 6, lines 2-10). The coated particles and binder are then placed in a gelatin capsule or in tablet form (Nadkarni, page 4, last two lines).

Staniforth (U.S. 5,004, 614) discloses a different technique for controlling rate release than does Nadkarni. Staniforth employs controlled release devices having a core including an active agent (e.g., drug) and an outer coating covering said core, which coating is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the release of the active agent during a dispensing period, thereby allowing the controlled release of the active agent through an orifice in the outer coating for a predetermined dispensing period (Staniforth, Abstract; column 3, lines 27-32; claim 1). Lamotrigine is nowhere mentioned.

Jain et al. (U.S. 2002/0012675) discloses controlled release nanoparticulate formulations comprising a poorly soluble nanoparticulate agent to be administered and a rate-controlling polymer which functions to prolong the release of the agent following administration, release time period ranging from 2 to 24 hours or longer (Jain, Abstract; claim 1). Lamotrigine is listed as a poorly soluble drug (page 4, paragraph 0047, lines 14-15). HPMC is named as a rate-controlling polymer (page 5, paragraph 0056, line 9).

Nadkarni and Staniforth both disclose core formulations which may have release-retarding excipients and which are additionally coated in membranes (including enteric membranes) which would further limit the release rate of the core formulations. Each core particle of Nadkarni may be coated in release rate limiting membranes depending on their solubility profiles and the core formulation of Staniforth is surrounded by a membrane with holes through which the core formulation is slowly dispersed.

In the currently claimed invention, lamotrigine is released in two phases. Lamotrigine is formulated into a matrix tablet with a modified release core surrounded by an enteric coat with holes in it. This allows the modified release core to be slowly released through the outer coating until the tablet passes onto the small intestine where the enteric coat dissolves releasing ALL the remaining core formulation. Therefore, the release of lamotrigine from the core formulation in the first phase (i.e., before the enteric coat dissolves) is slower than in the second phase when the enteric coat dissolves.

Figure 8 (sheets 10/12 and 11/12) shows the levels of lamotrigine in the serum from the human study of Example 7 using tablets as presently claimed (named DIFF (slow) (C, D) – with and without food) compared to those of the immediate release tablet (IR (A)) over 144 hours and 24 hours respectively. The serum levels measured in the volunteers dosed with the immediate release tablet shot up within an hour of dosing, stayed at this high level until about 4 hours after dosing, plateaued from approximately 10 to 24 hours after dosing and then steadily declined with time. The serum levels seen in volunteers dosed with tablets of the present invention took almost 10 hours to reach a much lower peak than the IR serum levels (comparably to the plateau levels of the IR after 10 hours) and then steadily declined with time. These figures show that the tablets of the present invention avoid the high peaks seen in serum levels when dosing with the IR tablet.

Figure 9 (sheet 12/12) shows the serum levels of lamotrigine from the human studies comparing the 200mg IR dose with a 200mg tablet according to the present invention. This also shows that the presently claimed tablet produces a slower rise in serum levels of lamotrigine over a 24 hour period than the IR tablet.

This data clearly displays that the two phases of lamotrigine release (the first slower than the second) provided by the tablet of the present invention results in serum levels that avoid the high peaks associated with the IR tablets.

Neither Staniforth nor Nadkarni provide a system wherein the lamotrigine /active is released in two phases, the first phase having a slower release rate

than the second. Nor does the combination of the teachings within Staniforth and Nadkarni achieve a slower first phase of release than the second. Combining Nadkarni with Staniforth results in having to formulate the multiparticulates (pellets) of Nadkarni into a compressed tablet which could then be coated by Staniforth's impermeable coat with a hole. The multiparticulates are then slowly released through the hole in the impermeable coating throughout the GI tract. Any additional control of the active's release from this dosage form would be dependent on the character of the rate-controlling membranes around each particle. As the release of the multiparticulates (no matter what they are coated in) is always governed by the rate-limiting step of exiting through the hole in the impermeable coating, there can never be a second phase of release faster than the first.

It is clear that only when armed with knowledge of the present invention can the person skilled in the art even hope to try and assemble it from the prior art and even then it is impossible to find all the elements in context from the two cited references. In desperation the Examiner has also cited Jain et al which discloses HPMC as a release-retarding excipient and this in dispute. Nadkarni lists HPMC as a possible release retarding excipient (Nadkarni at paragraph 038). Jain adds nothing to the Nadkarni and Staniforth disclosures.

Therefore, the claims are not obvious in view of the combination of Nadkarni, Staniforth, and Jain *et al.* for the reason that the prior art does not teach or suggest all Applicants' claim limitations.

Applicants respectfully submit that the Official Action fails to establish a prima facie case of obviousness with respect to each of the required elements and respectfully request reversal of the rejection. It is believed that the application is in condition for allowance. Therefore, reconsideration and allowance is requested.

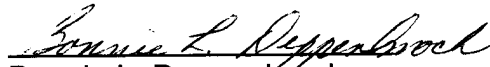
The Examiner has not acknowledged receipt of the certified copies of the priority documents. Applicants note that the copies were filed on July 29, 2003 in parent Application No. 10/629,177, now abandoned. It is believed that additional certified copies are not required in the present application. Applicants

respectfully request that the Examiner acknowledge receipt in the next Office communication.

Accordingly, it is respectfully requested that all rejections of the claims be reconsidered and withdrawn and that the application as amended be allowed.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,



Bonnie L. Deppenbrock
Attorney for Applicants
Registration No. 28,209

Date: 10 April 2008
Customer No. 23347
GlaxoSmithKline
Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Telephone: (919) 483-1577
Facsimile: (919) 483-7988